EXHIBIT 3

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Review Article

What Percentage of Chronic Nonmalignant Pain Patients Exposed to Chronic Opioid Analgesic Therapy Develop Abuse/Addiction and/or Aberrant Drug-Related Behaviors? A Structured Evidence-Based Review

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ABSTRACT

Design. This is a structured evidence-based review of all available studies on the development of abuse/addiction and aberrant drug-related behaviors (ADRBs) in chronic pain patients (CPPs) with nonmalignant pain on exposure to chronic opioid analgesic therapy (COAT).

Objectives. To determine what percentage of CPPs develop abuse/addiction and/or ADRBs on COAT exposure.

Method. Computer and manual literature searches yielded 79 references that addressed this area of study. Twelve of the studies were excluded from detailed review based on exclusion criteria important to this area. Sixty-seven studies were reviewed in detail and sorted according to whether they reported percentages of CPPs developing abuse/addiction or developing ADRBs, or percentages diagnosed with alcohol/illicit drug use as determined by urine toxicology. Study characteristics were abstracted into tabular form, and each report was characterized according to the type of study it represented based on the Agency for Health Care Policy and Research Guidelines. Each study was independently evaluated by two raters according to 12 quality criteria and a quality score calculated. Studies were not utilized in the calculations unless their quality score (utilizing both raters) was greater than 65%. Within each of the above study groupings, the total number of CPPs exposed to opioids on COAT treatment was calculated. Similarly, the total number of CPPs in each grouping demonstrating abuse/addiction, ADRBs, or alcohol/illicit drug use was also calculated. Finally, a percentage for each of these behaviors was calculated in each grouping, utilizing the total number of CPPs exposed to opioids in each grouping.

Results. All 67 reports had quality scores greater than 65%. For the abuse/addiction grouping there were 24 studies with 2,507 CPPs exposed for a calculated abuse/addiction rate of 3.27%. Within this grouping for those studies that had preselected CPPs for COAT exposure for no previous or current history of abuse/addiction, the percentage of abuse/addiction was calculated at 0.19%. For the ADRB grouping, there were 17 studies with 2,466 CPPs exposed and a calculated ADRB rate of 11.5%. Within this grouping for preselected CPPs (as above), the percentage of ADRBs was calculated at 0.59%. In the urine toxicology grouping, there were five studies (15,442 CPPs exposed). Here, 20.4% of the CPPs had no prescribed opioid in urine and/or a nonprescribed opioid in urine. For five studies (1,965 CPPs exposed), illicit drugs were found in 14.5%.

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Conclusion. The results of this evidence-based structured review indicate that COAT exposure will lead to abuse/addiction in a small percentage of CPPs, but a larger percentage will demonstrate ADRBs and illicit drug use. These percentages appear to be much less if CPPs are preselected for the absence of a current or past history of alcohol/illicit drug use or abuse/addiction.

Key Words. Pain; Chronic Nonmalignant Pain; Addiction; Drug Abuse; Aberrant Drug-Related Behaviors; Chronic Opioid Analgesic Therapy; Abuse/Addiction on Chronic Opioid Analgesic Therapy Exposure; Urine Toxicology

Introduction

Chronic opioid analgesic therapy (COAT) for intractable chronic pain has had a long history. In the 1970s the mantra was that chronic pain patients (CPPs) should be detoxified from opioids and that placement on opioids invariably led to addiction. In addition, there was lack of evidence for treatment of chronic intractable benign pain with opioids. This situation changed in the early 1980s, when researchers began to report that CPPs could be placed and maintained on opioids with clinical benefit and little or no development of addiction [1–20]. In addition, in the 1990s double-blind placebo-controlled studies began to appear, which indicated that opioids were effective analgesics in the treatment of chronic benign pain [21,22]. Since then, these trials and others have been analyzed in four meta-analyses [23–27]. The first two [23–25] demonstrated that opioids have analgesic efficacy for the treatment of neuropathic pain in intermediate-term studies. The third [26] demonstrated that weak and strong opioids outperformed placebo for improvement in pain and improvement in function in all types of chronic noncancer pain. In contrast, in the most recent meta-analysis, 105 of a small number of low back pain (only) [27] studies, the authors concluded that opioids may be efficacious for short-term pain relief, but that long-term efficacy (≥16 weeks) was unclear. They also concluded that substance-use disorders were common in CPPs taking opioids for back pain. There have also been a number of structured reviews of this literature. Here, Devulder et al. [28] determined that long-term opioid use in chronic nonmalignant pain patients improved their quality of life. Similarly, in another structured review, Bloodworth [29] concluded that opioids appear to improve overall function, including sleep. However, in a recent structured review, Nicholas et al. [30] concluded that functional outcomes are inconsistent across studies. In spite of these differing conclusions, the overall clinical opinion is that COAT improves pain and function in some CPPs.

As a result of these two convergent lines of data for efficacy with little addiction, COAT became commonplace and moved out of the pain medicine arena into other areas of medicine. However, in spite of the general acceptance for COAT, the issue of addiction development on COAT exposure was never fully settled. This is because studies that address the prevalence of addiction within CPPs [27,31] cannot be utilized to address the question of development of *de novo* addiction on opioid exposure. Portenoy [32] was the first to bring together and review [9] studies that looked at alleged addiction development on opioid exposure. He concluded that overall the literature indicated that addiction occurred as a result of two factors: the inherent reinforcing properties of the opioid drugs, and the psychological/social/physiological factors of the individual which predispose to addiction. He also concluded that these patient factors are uncommon in the chronic pain population [32]. No addiction percentages on opioid exposure were generated due to lack of studies and other technical problems. Since then, there have been three recent reviews addressing the issue of *de novo*/iatrogenic addiction on opioid exposure. In the first review, which was narrative in nature, Aronoff [33] concluded that appropriate opioid treatment does not cause drug addiction, but indiscriminate opioid treatment with patients at high risk for substance problems may cause drug addiction. No percentages were presented in this review. The second review was structured, but not evidence based and related to acute and subacute pain treatment with opioids. Here Wasan et al. [34] reviewed nine articles that they concluded related to iatrogenic addiction in patients treated for *acute or subacute pain*. They concluded that accurate data on the rate of addiction among inpatients administered opioids for acute pain do not exist. The third review [35] was also structured but not evidenced based. Here, Bartleson [35] con-

cluded that COAT was associated with a low risk of abuse or drug addiction. This conclusion was based on reviewing 11 reports, of which 3 mentioned or addressed addiction as a side effect of COAT treatment, and of these three, two indicated it to be a problem. According to these three reviews, information on *de novo*/iatrogenic addiction on opioid exposure was noted to be limited by lack of reliable scientific data. However, these three reviews did not systematically review all the COAT literature and did not utilize techniques that could generate percentages.

Portenoy [32] in the first review of studies in this area described what he termed aberrant drug-related behaviors (ADRBs). These are behaviors that can be observed in some COAT patients, which can operationally indicate the development of addiction [32,36]. As clinical experience with COAT grew, some authors reported that significant percentages [37–39] of CPPs demonstrated ADRBs with placement on COAT. Finally, with the development and standardization of COAT techniques, urine toxicologies came into standard use as a way of identifying some ADRBs. As a result, a number of publications [40–44] appeared, reporting on the results of these toxicologies in COAT patients.

The goal of this structured evidence-based review (described below) is then to review these three related lines of evidence (alleged addiction development on COAT exposure, development of ADRBs on COAT exposure, toxicology results with COAT patients) generated in the treatment of chronic benign nonmalignant (CBNM) pain on opioid exposure. It is hoped that such a distillation of the literature may shed some light on the question of whether addiction does or does not occur in CPPs with CBNM pain on opioid exposure (COAT), and if so, at what frequency or percentages. To the authors' knowledge, this is the first such review in the literature.

Methods

Relevant references were located by the following procedure. MEDLINE, Psychological Abstracts, Science Citation Index, and the National Library of Medicine Physician Data Query databases were reviewed utilizing the following subject headings: addiction, drug dependence, drug abuse, psychological dependence, craving, compulsive drug use, substance abuse, substance dependence, drug withdrawal, physical dependence, ADRBs, noncompliance, drug screens, urine toxicology screens, and chronic opioid analgesic treatment. Each of these was sequentially exploded with the medical subject headings (MESH) "opioids" and then "pain." Each term was exploded for subheadings in MESH and all retrieved references were reviewed. The searches were not restricted to the English language and conducted back to 1966, except for Science Citation Index, which was conducted back to 1974. The upper limit of each search was 2006. A manual search was also performed using key pain journals, pain meeting abstracts, and textbooks. For the following journals, the following years were reviewed: *Pain*, 1975–2006; *Spine*, 1976–2006; *The Pain Clinic*, 1986–2006; *Clinical Journal of Pain*, 1985–2006; and *Pain Medicine*, 2000–2006. Abstracts of the following meetings were reviewed for the following years: International Association for the Study of Pain 1981, 1984, 1987, 1990, 1993, 1996, 1999, 2002, and 2005, and the American Pain Society Meetings, 1982–2006. Three pain textbooks were reviewed for possible references. These were: Evaluation and Treatment of Chronic Pain, Third Edition, G. Aronoff (ed.), 1999; Handbook of Pain Management, Second Edition, C.D. Tollison, J.R. Satterthwaite, J.W. Tollison (eds.), 1994; and Textbook of Pain, Third Edition, P. Wall, R. Melzak (eds.), 1993. Seventy-nine references were found in this manner and were subjected to a cursory review. Studies were chosen for detailed review if they were not excluded through the use of the inclusion criteria listed below. Inclusion criteria were the following: patients placed on COAT for CBNM pain; and COAT treatment lasting over 1 month. This last criterion was initiated in order to ensure that there was no controversy over whether the patients were on the opioid long enough for addiction to develop. Studies not providing such information were excluded, e.g., Porter and Jick [13] and Chapman and Hill [45]. Studies were also excluded from detailed review if they related to tramadol (a nonscheduled weak opioid) [46] and any opioid antagonist [47]. These studies were excluded in order to avoid controversy as to the addictive potential of these drugs. Studies dealing with the prevalence of addiction/dependence within CPPs were also excluded, as these did not deal with actual placement on COAT, e.g., Fishbain et al. [31]. Studies were also excluded if not reporting a time interval for COAT exposure [4,39,48]. Also, studies [49] were excluded if, in the referral procedure for inclusion into the dataset, CPPs suspected of opi-

oid misuse were encouraged to be referred into the study group. This is selection bias (nonrandomness) and, as such, would not generate a true incidence for COAT drug abuse/addiction. Finally, studies such as Chabal et al. [38] were excluded because the numbers of patients exposed to COAT could not be determined. Of the 79 original references, 12 were excluded through the above exclusion criteria. The remaining 67 reports [1–3,5–12,14–22,27,37,40–44,50–89] were reviewed in detail. It is to be noted that some studies addressed more than one issue relating to this review. Those studies, if appropriate, were utilized more than once.

Studies were then sorted into the three relevant areas to this review described in the Introduction section: addiction development on exposure to opioids; demonstration of ADRBs on opioid exposure; and urine toxicology results of CBNM pain patients exposed to opioids. In reference to the urine toxicology studies, these broke down into two groups according to urine toxicology results: presence of a nonprescribed opioid and/or no prescribed opioid in urine; and illicit drug or alcohol in urine. Thus, urine toxicology reports were subsorted into these two groups. Finally, there was a group of studies in which CPPs had been exposed to opioids for over 1 month, but there was no mention in the results section of whether any CPPs had developed ADRBs and/or drug abuse/addiction by the end of the study. It could be argued that ADRBs and/or drug abuse/addiction was not mentioned, as these behaviors were absent. However, it could also be argued that they were not mentioned as they were not looked for. Thus, this group of studies was sorted into a separate grouping. Relevant data from all these studies was then abstracted by the senior author and grouped in tables according to the above groupings. The abstracted data were checked by one of the other authors (B.C.). The data in these tables were then utilized as the raw data to generate further information. These raw data tables are presented in Appendix Tables 1, 2, 2A, 3, and 4, to be found online on this journal's Website. The data in these tables are arranged to present the reference number/author/year, study question, design/type of study, sample size, results, type of evidence the study represented, quality score, and comments.

The categorization of the type of evidence the study represented was based on the guidelines developed by the Agency for Health Care Policy for categorizing the levels of evidence represented by reviewed studies (Appendix Table 5) [90]. Studies were categorized from I to V according to these guidelines. In these guidelines, I represents a meta-analysis of well-designed controlled studies and V represents a case report or clinical example.

The quality of the studies was categorized according to the systems developed by and reported by Hoogendoorn et al. [91] and De Vet et al. [92]. These researchers developed and tested a list of criteria to be used to assess methodological quality of prospective, historical cohort, placebo-controlled, and case–control studies. For details on how these criteria were developed, the reader is referred to the original studies [91,92]. Eleven criteria were selected from their list that were appropriate to the studies utilized. Hoogendoorn et al. [91] described 23 criteria, of which many related to outcome studies, for example, "Positive if the response after 1 year of follow-up was at least 80% of the number of participants at baseline, or if the non-response was not selective (data shown)." Thus, these criteria were not appropriate to the topic of this review and, as such, were not included in the criteria list utilized in this study. In addition, one of the 11 criteria (positive if the data were collected by means of standardized methods of acceptable quality) was duplicated to address two relevant issues to this review: how was addiction diagnosed (criterion 6), and what type of list was utilized to generate the presence of ADRBs (criterion 7). This resulted in a total of 12 criteria, which are presented in Appendix Table 6. For each included study, each criterion was rated as either present/fulfilled (+), not present/unfulfilled (–), or not applicable (NA). NA was utilized as follows. There were basically four types of studies analyzed for quality: case–control, cohort, correlational, and experimental (would include placebo controlled). Thus, some criteria in Appendix Table 6 pertained only to case–control studies, while others applied only to cohort studies, and so on. As such, NA was utilized if the criterion in question pertained to another type of study other than the one being reviewed. In addition, NA was utilized when that criterion did not pertain to the study in question. NA was not utilized when information was not available or not described [93]. A negative was assigned if the item did not meet the preselected criteria [93]. Each study was rated independently for each applicable criterion by the senior author (D.F.) and another author (B.C.). Each of these raters placed either a positive, negative, or NA for each criterion for each study selected for detailed review. The assigned categorizations by D.F. and B.C. for each selected study

were then compared in a meeting. Any discrepancies in the categorizations were than resolved by mutual agreement. This resulted in a final decision as to whether each criterion received a negative, positive, or NA categorization. Categorizations were then summarized and placed into tabular format (Appendix Table 6).

A quality score was obtained by counting the number of positives obtained. This score was divided by 12 minus the number of NAs and multiplied by 100, which gave the percent quality score. Studies scoring less than 50% have been historically rated as "low quality" [93]. These studies are usually not utilized to arrive at conclusions about a review topic. For the purposes of this review, however, we arbitrarily set the acceptable quality score at 65%. Studies scoring less than 65% were not utilized in arriving at a conclusion about the reviewed topic.

Utilizing data for each of the Appendix Tables 1, 2, 2A, 3, and 4, calculations were made for the following variables combining all the CPPs exposed to COAT in the studies in that grouping: reported addiction percentage; opioid exposure time; percentages of types of terms utilized to describe the concept of addiction; studies' quality characteristics; reported abuse/addiction percentages by whether studies had or had not selected patients on previous/current history of alcohol/illicit drug use; ADRBs percentage; % of studies by types of methods for identification of ADRBs; reported ADRBs percentages by whether studies had or had not selected patients on previous/current history of alcohol/illicit drug use; illicit drug use percentage calculations; and urine toxicology-reported illicit drug use percentages by whether studies had or had not selected patients on previous/current alcohol/illicit drug use. These data are summarized and presented in Tables 1–3 according to the above heading. As noted above, there was a group of studies that had exposed patients to COAT, but which did not specifically mention the absence/presence of addiction and/or ADRBs on opioid exposure. The above calculations for this group were also performed taking it for granted that nonmention of ADRBs and addiction

Table 1 Percentages of abuse/addiction on chronic opioid analgesic therapy (COAT) exposure derived from clinical opinion studies addressing this area

Addiction percentage calculations	
1. # of studies	24
2. Total # of patients exposed in all studies combined	2,507
3. % range of alleged reported addition in the 23 studies	0–45
4. Total # of patients allegedly "addicted" for all studies combined	82
5. Average percentage of alleged "addiction" for all studies combined	3.27
Opioid exposure time calculations	
1. Range of opioid exposure time in the 23 studies	2–240 months
2. Average opioid exposure time calculated according to the percentage of patients each study represented out of total # of patients exposed	26.2 months
Percentages of types of terms utilized to describe the concept of addiction in the 23 studies	
1. # of studies where abuse term utilized	9 (37.5%)
2. # of studies where addiction term utilized	12 (50.0%)
3. # of studies where other terms utilized (psychological dependence, drug problem, drug craving, overreliance on medication, drug seeking)	6 (25.0%)
Studies' quality characteristics	
1. % retrospective	17 (70.8%)
2. % prospective or randomized	7 (29.2%)
3. Number of studies within each type of evidence category	
a. Type 2 [2,12,16]	3 (12.5%)
b. Type 3 [11,17,18,51,74,88]	6 (25.0%)
c. Type 4 [1,3–10,14,15,19,37,57,58,61]	15 (62.5%)
4. Average quality score	76.2%
Reported abuse/addiction percentages by whether studies had or had not selected patients on previous/current history of alcohol or illicit drug use	
1. % of studies not selecting	66.7
2. % of studies where selection not stated	16.6
3. % of studies selecting	16.6
4. % of studies also selecting for no previous opioid exposure	4.3
5. % of abuse/addiction within the not-selecting group	5.0
6. % of abuse/addiction in the not-stated group	5.8
7. % of abuse/addiction in the selecting group [11,12,18,88]	0.19
8. % of abuse/addiction in the selecting for no previous opioid exposure [12]	4.35
9. % of abuse/addiction in the combined not-selecting and not-stated groups	5.4

Table 2 Percentages of aberrant drug-related behaviors (ADRBs)

2A. Derived from studies addressing this area	
ADRBs percentage calculations	
1. # of studies	17
2. Total # of patients exposed in all studies combined	2,466
3. % range of ADRBs reported for 17 studies	0–44.6
4. Total # of patients demonstrating 1 or more ADRBs for all studies combined	286
5. Average percentage of ADRBs for all studies combined	11.5
Opioid exposure time calculations	
1. Range of opioid exposure time in the 17 studies	1–34 months
2. Average opioid exposure time calculated according to the percentage of patients each study represented out of total # of patients exposed	10.8 months
% of studies by types of methods for identification of ADRBs	
1. Specific ADRBs reported only	15 (83.3%)
2. Lists of ADRBs utilized [37,65,106]	3 (15.7%)
3. Average percentage of ADRBs for specific ADRBs reported only group	34.1%
4. Average percentage of ADRBs for list of ADRBs utilized group	1.3%
Studies' quality characteristics	
1. % retrospective	8 (44.4%)
2. % prospective or randomized	10 (55.6%)
3. Number of studies within each type of evidence category	
a. Type 2 [12,53,77]	3 (16.6%)
b. Type 3 [11,37,54,59,61,65,68,74,75,87,106]	11 (61.1%)
c. Type 4 [50,52,56,63]	4 (22.3%)
4. Average quality score	75.3%
% ADRBs by whether studies had or had not selected patients on previous/current history of alcohol/illicit drug use	
1. % of studies not selecting [50,52,56,59,61,65,68,74,87,106]	10 (55.5%)
2. % of studies where selection not stated [37,54,63]	3 (16.6%)
3. % of studies selecting [11,12,53,75,77]	5 (27.8%)
4. % of studies selected for no previous exposure to opioids	0 (0%)
5. % of ADRBs for the not-selected group	11.2%
6. % of ADRBs for the not-stated group	21.6%
7. % of ADRBs for the selecting group	0.59%
8. % of ADRBs for the selecting and not-stated groups	16.1%
2B. Derived from urine toxicology studies (no opioid or opioid in urine other than prescribed ADRBs percentage calculations)	
1. # of studies	5
2. Total # of patients exposed	15,442
3. % range of ADRBs reported for the 4 studies	13–40
4. Total # of patients demonstrating one ADRB by urine toxicology	3,150
5. Average percentage of ADRBs for all studies combined	20.4
Opioid exposure time calculations	
1. Range of opioid exposure time in the 4 studies (unknown 2 studies [42,44]).	8–36 months
2. Average opioid exposure time calculation according to the percentage of patients each study represented out of total # of patients exposed	22.1 months
% of studies by types of methods for identification of ADRBs	
1. By urine toxicology	5 (100%)
Studies' quality characteristics	
1. % retrospective	1 (20.0%)
2. % prospective	4 (80.0%)
3. Number of studies within each type of evidence category	
a. Type 2	0%
b. Type 3 [41,43,44]	3 (60.0%)
c. Type 4 [42,89]	2 (40.0%)
4. Average quality score	84.3%
% ADRBs by whether studies had or had not selected patients on previous/current history of alcohol/illicit drug use	
1. % of studies not selecting [41–44,89]	5 (100%)

meant that these behaviors were absent. These data are presented in Table 4. Finally, data from Table 4 were added to data in Tables 1 and 2, and these data are presented in Tables 5 and 6, respectively.

Results

The results of this evidence-based review are summarized in Tables 1–6. Relevant findings are the following:

Table 3 Percentages of illicit drug use derived from urine toxicology studies

Illicit drug use percentage calculation	
1. # of studies	5
2. Total # of patients exposed	1,965
3. % range of illicit drug use reported	4.3–57
4. Total # of patients demonstrating illicit drugs in urine	285
5. Average percentage of patients with illicit drugs in urine for all studies combined	14.5
Opioid exposure time calculations	
1. Range of opioid exposure time in the 2 studies (unknown for 3 studies [40,44,89])	36 months
% of studies by type of method for identification of illicit drug use	
1. By urine toxicology	100%
Studies' quality characteristics	
1. % retrospective	2 (40%)
2. % prospective	3 (60%)
3. # of studies within each evidence category	
a. Type 2	0%
b. Type 3 [43,44,84]	3 (60%)
c. Type 4 [40,89]	2 (40%)
4. Average quality score	84.2%
Reported illicit drug use percentages by whether studies had or had not selected patients on previous/current history of alcohol/illicit drug use	
1. % of studies not selecting	5 (100%)

Table 1

Average percentage of reported "addiction" development on COAT exposure for 24 studies or 2,507 CPPs exposed was 3.27%. Here the average exposure time was 26.2 months and the most frequent term utilized was "addiction" at 50.0%. Most of these studies were retrospective (70.8%) and the average quality score was 76.2%. Only 16.6% of these studies had preselected patients for no current and/or past history of alcohol/illicit drug abuse/addiction. Percentage of abuse/addiction in the preselected group was calculated at 0.19% vs 5.0% within the not-selected group. Percentage of abuse/addiction in the selected group for no previous opioid exposure was 4.35%.

Table 2A

Average percentage of ADRBs noted on COAT exposure for 17 studies and 2,466 CPPs exposed was 11.5%. Here the average exposure time was 10.8 months, and the most frequent method (83.3%) of identifying ADRBs was reporting of specific ADRBs only. Most of these studies were prospective (55.6%) and the average quality score was 75.3%. Only 27.8% of these studies had

Table 4 Percentages of abuse/addiction on chronic opioid analgesic therapy (COAT) exposure derived from studies in which absence/presence, abuse/addiction, and aberrant drug-related behaviors (ADRBs) on opioid exposure not specifically mentioned

Addiction and ADRB percentage calculation	
1. # of studies	24
2. Total # of patients exposed in all studies combined	10,344
3. % range of addiction or ADRBs for 20 studies	0
4. Total # of patients demonstrating addiction or ADRBs for all studies combined	0
5. Average percentage of addiction or ADRBs for all studies combined	0
Opioid exposure time calculation	
1. Range of opioid exposure time in the 20 studies	1–48 months
2. Average opioid exposure time calculated according to the percentage of patients each study represented out of total # of patients exposed	11.4 months
Percentages of types of terms utilized to describe the concept of addiction or ADRBs	
1. Not applicable as not mentioned in any of these studies	
Studies' quality characteristics	
1. % retrospective	0 (0%)
2. % prospective	24 (100%)
3. Number of studies within each type of evidence category	
a. Type 2 [21,22,27,60,64,67,69–72,79,80,82,85,86]	15 (62.5%)
b. Type 3 [22,55,62,66,73,76,78,81,83]	9 (37.5%)
4. Average quality score	80.1%
Reported abuse/addiction percentages by whether studies had or had not selected patients on previous/current history of alcohol/illicit drug use	
1. % of studies not selecting [22,66,76,79,83,86]	7 (29.1%)
2. % of studies where selection not known	17 (70.9%)
3. % of studies selecting	0 (0%)
4. % of studies selected for no previous opioid exposure	1 (5%)
5. % of abuse/addiction or ADRBs within any above groups	0%

Table 5 Combining patients exposed in Table 1 and Table 4

Addiction percentage calculations	
1. # of studies	48
2. Total # of patients exposed in all studies combined	12,851
3. % range of alleged reported addiction in the 43 studies	0–45
4. Total # of patients allegedly "addicted" for all studies combined	82
5. Average percentage of alleged "addiction" for all studies combined	0.63
Opioid exposure time calculations	
1. Range of opioid exposure time in the 43 studies	1–240 months
2. Average opioid exposure time calculated according to the percentage of patients each study represented out of total # of patients exposed	17.3 months
Percentages of types of terms utilized to describe the concept of addiction or new ADRBs where determined	
1. Not applicable	
Studies' quality characteristics	
1. % retrospective	17 (35.4%)
2. % prospective or randomized	31 (64.6%)
3. Number of studies within each type of evidence category	
a. Type 2	18 (37.5%)
b. Type 3	15 (31.3%)
c. Type 4	15 (31.2%)
4. Average quality score	78.2%
Reported abuse/addiction percentages by whether studies had/had not selected patients on previous/current history of alcohol/illicit drug use	
1. % of studies not selecting	19 (39.6%)
2. % of studies where selection not stated	4 (8.3%)
3. % of studies selecting	25 (52.1%)
4. % of studies selected for no previous opioid exposure	2 (4.2%)
5. % of abuse/addiction in the not-selecting groups	1.8%
6. % of abuse/addiction in the not-stated groups	5.8%
7. % of abuse/addiction in the selecting groups	0.07%
8. % of abuse/addiction in the selecting for no previous exposure to opioids [15]	0.28%
9. % of abuse/addiction in the combined not-selecting and not-stated groups	3.0%

Table 6 Combining patients exposed in Table 2 and Table 4

ADRBs calculations	
1. # of studies	42
2. Total # of patients exposed in all studies combined	12,810
3. % range of alleged reported addiction in the 37 studies	0–44
4. Total # of patients demonstrating 1 or more ADRBs in all studies combined	286
5. Average percentage of ADRBs in all studies combined	2.2
Opioid exposure time calculations	
1. Range of opioid exposure time in the 37 studies	1–48 months
2. Average opioid exposure time calculated according to the percentage of patients each study represented out of total # of patients exposed	13.8 months
Percentages of studies by types of methods for identifying ADRBs	
1. Not applicable	
Studies' quality characteristics	
1. % retrospective	8 (19.1%)
2. % prospective/randomized	34 (80.9%)
3. Number of studies within each type of evidence category	
a. Type 2	18 (42.9%)
b. Type 3	20 (47.6%)
c. Type 4	4 (9.5%)
4. Average quality score	78.1%
% reported ADRBs percentages by whether studies had or had not selected patients on previous/current history of alcohol/illicit drug use	
1. % of studies not selecting	17 (40.5%)
2. % of studies where selection not stated	3 (7.1%)
3. % of studies selecting	22 (52.4%)
4. % of studies selected for no previous opioid exposure	1 (2.7%)
5. % of ADRBs within the not-selecting groups	11.2%
6. % of ADRBs within not-stated groups	21.6%
7. % of ADRBs within the selecting groups	0.1%
8. % of ADRBs within the selecting for no previous opioid exposure group	0%
9. % of ADRBs within the combined not-selecting and not-stated groups	16.1%

preselected patients for COAT. Percentage of ADRBs for the preselected group was calculated at 0.59% vs 11.2% within the not-selected group and 21.6% for the nonstated group.

Table 2B

Average percentage of ADRBs determined by urine toxicology for five studies of 15,442 CPPs exposed to COAT was 20.4%. Here the average exposure time was 22.1 months. Most of these studies (80%) were prospective and the average quality score was 84.3%. None of the studies had preselected their CPPs.

Table 3

Average percentage of illicit drug use determined by urine toxicology for five studies of 15,442 CPPs exposed to COAT was 14.5%. Here exposure time was 36 months for one study on which information was available. Most of these studies were prospective (60.0%) and the average quality score was 84.2%. None of the studies had preselected their CPPs.

Table 4

Average percentage of "addiction" development in 24 studies (10,344 CPPs exposed) where there was no specific mention of presence/absence of this issue was 0%. Here the average exposure time was 11.4 months. One hundred percent of these studies were prospective and the average quality score was 80.1%%. A total of 70.9% of these studies had preselected their patients.

Table 5

Average percentage of alleged "addiction" development on COAT exposure for 48 studies or 12,851 CPPs exposed was 0.63%. Here the average exposure time was 17.3 months. Most of these studies were prospective (64.6%) and the average quality score was 78.2%. Here 52.1% of the studies had preselected their CPPs. Percentage of abuse/addiction in the selected group was 0.07%.

Table 6

Average percentage of ADRBs noted on COAT exposure for 41 studies and 12,810 CPPs exposed was 2.2%. Here the average exposure time was 13.8 months. Most of these studies were prospective (80.9%) and the average quality score was 78.1%. Here 52.4% of the studies had preselected their CPPs. Percentage of ADRBs in the selected group was 0.1%.

Discussion

A number of observations can be derived from the results of this evidence-based review presented in Tables 1–6. First, the reported incidence of opioid abuse/addiction on COAT exposure as calculated here appears to be quite low (3.27%) (Table 1). This number is well below the accepted prevalence of addictions (approximately 10%) in the general population. Second, the calculated average exposure time to COAT is well above 1 month for all the derived groupings (Tables 1–4). Third, although the quality of the studies in each grouping (Tables 1–4) was generally over 70% in some of the groupings, the majority of the studies were retrospective (Tables 1 and 2). Fourth, the incidence of ADRBs (11.5%) is greater than the incidence of clinician determined presence of abuse/addiction (3.27%). Fifth, it is interesting to note that the percentage of alleged abuse/addiction and percentage of ADRBs was lower within the grouping for the preselected subgroups (no history of addiction/abuse or current history of illicit drug use) vs the nonselected subgroups (Tables 1 and 2A). In the case of the abuse/addiction grouping it was 3.27% (nonselected) vs 0.19% (selected) (Table 1). For the case of the ADRBs grouping, it was 11.5% (nonselected) vs 0.59% (selected) (Table 2A). Sixth, it is also interesting to note that preselecting for no previous history of opioid exposure may not confer protection against development of alleged addiction/abuse, i.e., 3.27% (not selecting) and 4.35% (selecting) (Table 1). Seventh, it appears that urine toxicology identifies a greater percentage (20.4%; Table 2B) of CPPs demonstrating ADRBs (no opioid or opioid in urine other than prescribed) vs ADRBs identified by observation only (11.5%; Table 2A). Eighth, illicit drug use is present in 14.5% (Table 3) exposed to COAT. This again is within the range of the prevalence of addictive disease within the general population (10%). Nine, as expected, the addition of the patients in Table 4 to those of Tables 1 and 2A lowered the incidence of addiction/abuse to 0.63% from 3.27% and of ADRBs from 11.5% to 2.2%. Some of these observations will be discussed below in relationship to previous literature.

In the first review of the prevalence (not *de novo*) of reported abuse/addiction within CPPs, Fishbain et al. [31] pointed out that this research area was confounded by a lack of agreement as to how to arrive at a diagnosis of addiction. This problem with terminology has since been echoed by other

researchers [94,95]. Taking a closer look at the results of this current evidence-based structured review, it appears that within the abuse/addiction studies grouping (Table 1), various terms were utilized to indicate addiction, such as abuse, drug problem, drug seeking, etc. In none of the studies was an actual operational diagnosis for substance dependence utilized. Only two studies utilized the correct concepts for addiction [31] (psychological dependence, craving), but it is unclear how these were derived operationally. Besides being a confounder to the reported results here, how can this issue impact on the derived results? In one scenario it is believed that not utilizing operational criteria may increase the incidence or the likelihood of making that diagnosis. As such, it is likely that the calculated incidence of 3.27% for abuse/addiction could have been lower if recognized criteria were systematically utilized.

Variables that have been found in the addiction and pain literature to predict ADRBs are the following: previous history of alcohol/illicit drug use [96]; current history of alcohol/illicit drug use [96]; family history for alcohol/illicit drug use [96]; treatment in a drug rehabilitation facility [97]; use of multiple drugs [98]; use of needles [98,99]; and being a smoker [96]. Predisposition to addiction is likely genetically determined [93,100], and hence the importance of the family history for alcohol/illicit drug use and previous history and current history of alcohol/illicit drug use. As such, it is not surprising that if you preselect patients for COAT without these variables, you are likely to have fewer ADRBs in your COAT group. This was postulated by Aronoff [33] and is supported by our findings (above) for differences between preselected and nonselected CPPs for abuse/addiction and ADRBs on COAT exposure. Finally, this part of the data supports the concept that *de novo* addiction (addiction without a previous history of addiction) may be extremely rare on COAT exposure. In this study it was calculated to be 0.19% for the abuse/addiction grouping (Table 1), and even lower (0.07%; Table 5) if the studies in Table 4 are utilized.

As noted in the Introduction, ADRBs can be a red flag for the development of addiction in COAT treatment. In this study the frequency of ADRBs was consistently higher (Table 2A) than that for clinician-determined presence of abuse/addiction (Table 1). At issue then is whether ADRBs represent the true incidence of addiction within COAT treatment, and if not, which ADRBs do? Unfortunately, the "norms" for ADRBs have not been clearly established [101]. It is likely that these behaviors exist along a continuum with certain behaviors being less aberrant (such as aggressively requesting medications), with other behaviors being more aberrant, such as frequent unsanctioned dose escalation [94], with some behaviors, such as injecting prescribed medications, being most aberrant [101]. Thus, it is unlikely that all ADRBs are equally indicative of addiction, and as such, the calculated incidence for ADRBs (11.5%; Table 2A) is likely an overestimate for the concept of addiction development on exposure. Therefore, this issue serves as a confounder to this part of the study in trying to determine the incidence of abuse/addiction on COAT exposure.

Pseudo-addiction refers to ADRBs, such as dose escalation, which appear to indicate the possibility of addiction, but which stop if pain is adequately controlled, thus indicating that they were not part of the addiction syndrome [102]. As the original report [102] was a case study, this concept lacked significant evidence. Recently, however, there have been a number of studies that have been able to identify the presence of this syndrome [69,103,104]. At issue then is what impact the concept of pseudo-addiction could have on the results of this study. Pseudo-addiction could present as some ADRBs, e.g., dose escalation, medication hoarding, etc. As such, within the reported prevalence of ADRBs in the reviewed studies, some CPPs could have been demonstrating pseudo-addiction. None of the reviewed ADRBs studies had considered the possibility of pseudo-addiction. Thus, the reported prevalence of addiction in these studies could well have been lower, thus confounding the results of our study. Similar observations also apply to the abuse/addiction grouping, as often these diagnostic labels are placed on the patient upon observing ADRBs.

As noted above, the prevalence of ADRBs identified by urine toxicology was higher by urine toxicology (20.4%) than by observation only (11.5%). This finding has previously been reported by other researchers [43,105]. Thus, our results support and are supported by this previous work.

What are some additional potential confounders to the results of this evidence-based structured review? First, a significant percentage of the studies in the abuse/addiction grouping were retrospective. Retrospective studies, unless there are specific criteria utilized for clinical observation, can under- or overreport the presence of the clinical problems being studied. Second, it is not clear

whether addiction development is determined by time of exposure and/or opioid dose. As noted in Methods, time of exposure was controlled for and all study groupings had very significant exposure times. However, opioid dose was not controlled for. This is because in many of the reviewed opioid exposure studies, opioid doses were not reported. Presently, it is unclear whether there is some opioid dose that is necessary to develop addiction. If this is the case, then the dose issue would serve as a confounder to the results of this study. Third, this evidence-based structured review had inclusion/exclusion criteria. These inclusion/exclusion criteria were chosen to minimize confounding by studies which would not generate reliable percentages for abuse/addiction or ADRBs on opioid exposure. Thus, for example, studies were excluded if CPPs were not maintained on opioids for more than 1 month. This was performed to make sure that, if abuse/addiction was to develop, that exposure time was not inappropriately short, thus precluding this possibility. Similarly, trials were not included if a weak opioid (tramadol) was utilized, as it has been shown that this drug is associated with little abuse. However, these inclusion/exclusion criteria could have eliminated studies in which little abuse/addiction would have been noted and/or that were high-quality studies. As such, it is possible that these inclusion/exclusion criteria could have inflated the abuse/addiction or ADRBs percentages. However, we believe that these inclusion/exclusion criteria were appropriate and necessary according to the current state of scientific knowledge and thus improved the quality of the data generated. We would suggest that future researchers utilize the same inclusion/exclusion criteria in studying this research area.

Finally, it is unclear whether utilizing the studies in Table 4 adds useful information or becomes a confounder to the data. As noted above, in the studies presented in Table 4, CPPs were exposed to opioids for extended periods of time. The quality of these studies in general is better than the other studies in this review, as most of them are double-blind placebo controlled. The vast majority of these studies had preselected their CPPs for inclusion by eliminating CPPs with a previous or current history of drug/alcohol abuse/addiction. Yet, it is unclear whether these studies monitored CPPs for the development of abuse/addiction or ADRBs over the course of the studies, as no data on this issue were reported. Thus, it is possible that some of these studies could have had some CPPs who developed ADRBs and/or abuse/addiction. Therefore, the supposed 0% incidence of ADRBs and abuse/addiction within this study grouping could be an underestimate. This is the reason why these studies were isolated from the other studies as a subgroup. Thus, the results generated in Tables 4–6 should be viewed with caution. At issue then is whether these kinds of trials are able to detect ADRBs? To our knowledge, this question has not been addressed in the literature. In our opinion, these trials should be able to detect ADRBs if they choose to. It is encouraging that there have been some recent industry-sponsored trials [88] that have specifically looked for abuse/misuse. In our opinion, because of the financing behind the industry-sponsored trial, researchers here should be in a better position to identify ADRBs than the individual clinician performing a clinical study.

What are the clinical implications of this study? First, if the results of this evidence-based structured review are correct, the pain clinician can be relatively certain that opioid exposure will lead to abuse/addiction in a relatively low percentage of CPPs. This statement is based on the fact that this dataset contained a large number of CPPs exposed to COAT. Second, the chances of iatrogenic abuse/addiction development can be significantly decreased by preselecting CPPs. Although this idea has been clinical lore, the presented data to date are the best evidence for this view. Third, to fully capture the incidence of abuse/addiction and ADRBs in their COAT samples, clinicians should routinely utilize ADRB lists and urine toxicology.

Finally, according to this review, how can this area of research be improved? First, research clinicians should concentrate on performing prospective studies in this area. Second, these studies should have the following characteristics: 1) clearly documented opioid exposure times; 2) clearly documented opioid doses at which abuse/addiction and/or ADRBs were noted; 3) if utilizing the abuse/addiction concept, clearly defined definitions or diagnostic criteria by which such conclusions were reached; 4) ADRB lists should be utilized to facilitate documentation and observation; 5) urine toxicology should be utilized in all these studies to ensure that no ADRBs are missed, thus adding to the validity of the results; and 6) documentation as to whether CPPs were preselected and what were those criteria. Finally, industry opioid efficacy studies should monitor for abuse/addiction and ADRB development utilizing specific criteria and ADRB lists, even if the CPPs included in these studies are preselected for no abuse/addiction.

Conclusions

The results of this evidence-based structured review indicate that COAT exposure will lead to abuse/addiction in a very small percentage of patients. This percentage can be dramatically decreased by preselecting CPPs for no previous or current history of drug/alcohol abuse/addiction.

Supplementary Material

The following supplementary material is available for this article:

Appendix Table 1 Is there abuse/addiction with exposure to coat as indicated by clinician opinion?

Appendix Table 2 Is there addiction with exposure to COAT as indicated by development of aberrant drug-related behaviors (ADRBs)?

Appendix Table 2A Is there addiction with exposure to COAT as indicated by aberrant drug related behaviors identified by urine toxicology (no prescribed opioid in urine, other opioids than prescribed?

Appendix Table 3 Is there addiction with exposure to COAT as indicated by aberrant by urine toxicology (illicit drugs in urine)?

Appendix Table 4 Studies which do not address addiction or aberrant drug-related behaviors directly

Appendix Table 5 Levels of evidence as applied by the AHCPR for guideline development [90]

Appendix Table 6 Summary table of quality ratings for each study

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References

1 Dunbar SA, Katz NP. Chronic opioid therapy for nonmalignant pain in patients with a history of substance abuse: Report of 20 cases. J Pain Symptom Manage 1996;11:163–71.

2 Cowan DT, Wilson-Barnett J, Griffiths P, et al. A randomized, double-blind, placebo-controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine. Pain Med 2005;6:113–21.

3 Tennant FS Jr, Uelmen GF. Narcotic maintenance for chronic pain. Medical and legal guidelines. Narc Maintenance 1983;73:81–94.

4 Tennant F, Robinson D, Sagherian A, Seecof R. Chronic opioid treatment of intractable, nonmalignant pain. Pain Manage 1988;Jan/Feb:18–26.

5 Taub A. Opioid analgesics in the treatment of chronic intractable pain of non-neoplastic origin. In: Kitahata LM, Collins JD, eds. Narcotic Analgesics in Anesthesiology. Baltimore, MD: Williams & Wilkins; 1982:199–208.

6 Portenoy RK. Chronic opioid therapy in nonmalignant pain. J Pain Symptom Manage 1990;5:46–62.

7 Tennant FS, Robinson D, Sagherian A, et al. Chronic opioid treatment of intractable, nonmalignant pain. NIDA Res Monogr 1988;81:174–80.

8 Schaffer-Vargas G, Schaffer S, Mejia A, Fernandez C. Opioid for non-malignant pain experience of Venezuelan Center, 9th World Congress on Pain. 1999;289:345.

9 Urban BJ, France RD, Steinberger EK, Scott DL, Maltbie AA. Long-term use of narcotic/antidepressant medication in the management of phantom limb pain. Pain 1986;24:191–6.

10 Zenz M, Strumpf M, Tryba M. Long-term oral opioid therapy in patients with chronic nonmalignant pain. J Pain Symptom Manage 1992;7:69–77.

11 Milligan K, Lanteri-Minet M, Borchert K, et al. Evaluation of long-term efficacy and safety of transdermal fentanyl in the treatment of chronic noncancer pain. J Pain 2001;2:197–204.

12 Moulin DE, Iezzi A, Amireh R, et al. Randomised trial of oral morphine for chronic non-cancer pain. Lancet 1996;347:143–7.

13 Porter J, Jick HN. Addiction rare in patients treated with narcotics. N Engl J Med 1980;302:123.

14 Doquang-Cantagrel N, Magnuson SK, Wallace MS. Tolerability and efficacy of opioids in chronic nonmalignant pain. Addiction 1991;722:129.

15 Bouckoms AJ, Masand P, Murray GB, et al. Chronic nonmalignant pain treated with long-term oral narcotic analgesics. Ann Clin Psychiatry 1992;8:185–92.

16 Jamison RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain. A randomized prospective study. Spine 1998;23:2591–600.

17 France RD, Urban BJ, Keefe FJ. Long-term use of narcotic analgesics in chronic pain. Soc Sci Med 1984;19:1379–82.
18 Kell MJ. Long-term methadone maintenance for intractable, nonmalignant pain: Pain control and plasma opioid levels. AJPM 1994;4:10–6.
19 Cowan DT, Wilson-Barnett J, Griffiths P, Allan LG. A survey of chronic noncancer pain patients prescribed opioid analgesics. Pain Med 2003; 4:340–51.
20 Mullican WS, Lacy JR. Tramadol/acetaminophen combination tablets and codeine/acetaminophen combination capsules for the management of chronic pain: A comparative trial. Clin Ther 2001;23:1429–44.
21 Caldwell JR, Hale ME, Boyd RE, et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal anti-inflammatory drugs: A double blind, randomized, multicenter, placebo controlled trial. J Rheumatol 1999;26:4.
22 Kjaersgaard-Andersen P, Nafei A, Skov O, et al. Codeine plus paracetamol versus paracetamol in longer-term treatment of chronic pain due to osteoarthritis of the hip. A randomized, double-blind, multi-centre study. Pain 1990;43:309–18.
23 Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. Pain 2004;112:372–80.
24 Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: Systematic review and meta-analysis of randomized controlled trials. JAMA 2005;293:3043–52.
25 Eisenberg E, McNicol E, Carr DB. Opioids for neuropathic pain. Cochrane Database Syst Rev 2006;3:CD006146.
26 Furlan A, Sandoval J, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: A meta-analysis of effectiveness and side effects. CMAJ 2006;174:1589–94.
27 Martell BA, O'Connor PG, Kerns RD, et al. Systemic review: Opioid treatment for chronic back pain; prevalence, efficacy, and association with addiction. Ann Intern Med 2007;146:116–27.
28 Devulder J, Richarz U, Nataraja SH. Impact of long-term use of opioids on quality of life in patients with chronic nonmalignant pain. Curr Med Res Opin 2005;21:1555–68.
29 Bloodworth D. Issues in opioid management. Am J Phys Med Rehabil 2005;84:S42–55.
30 Nicolas MK, Molloy AR, Brooker C. Using opioids with persisting noncancer pain: A biopsychosocial perspective. Clin J Pain 2006;22:137–46.
31 Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence and addiction in chronic pain patients. Clin J Pain 1992;8:77–85.
32 Portenoy R. Opioid therapy for chronic nonmalignant pain: A review of the critical issues. J Pain Symptom Manage 1996;11:203–17.
33 Aronoff G. Opioids in chronic pain management: Is there a significant risk of addiction? Curr Rev Pain 2000;4:112–21.
34 Wasan A, Correll D, Kissin I, O'Shea S, Jamison R. Iatrogenic addiction in patients treated for acute or subacute pain: A systematic review. J Opioid Manage 2006;2:16–22.
35 Bartleson JD. Evidence for and against the use of opioid analgesics for chronic nonmalignant low back pain: A review. Pain Med 2002;3:260–71.
36 Jaffee J. Opiates: Clinical aspects. In: Lowenson J, Ruiz P, Mullman R, eds. Substance Abuse, A Comprehensive Text. Baltimore, MD: Williams & Wilkins; 1992:186–94.
37 Passik SD, Kirsh KL, Whitcomb L, et al. Monitoring outcomes during long-term opioid therapy for noncancer pain: Results with the pain assessment and documentation tool. J Opioid Manage 2005;1:5.
38 Chabal C, Erjavec M, Jacobson L, Mariano A, Chaney E. Prescription opiate abuse in chronic pain patients: Clinical criteria, incidence, and predictors. Clin J Pain 1997;13:150–5.
39 Manchikanti L, Fellows B, Damron KS, Pampati V, McManus CE. Prevalence of illicit drug use among individuals with chronic pain in the Commonwealth of Kentucky: An evaluation of patterns and trends. J Ky Med Assoc 2005;103:55–62.
40 Vaglienti RM, Huber SJ, Noel KR, Johnstone RE. Misuse of prescribed controlled substances defined by urinalysis. W V Med J 2003;99:67–70.
41 Schulzeck S, Gleim M, Maier C. Factors contributing to the results of long-term treatment with oral morphine tablets in patients with chronic nonmalignant pain. Anaesthetist 1993;42:545–56.
42 Kell M. Monitoring compliance with OxyContin Rx in 14,712 patients treated in 127 outpatient pain centers. Pain Med 2005;6:186–7.
43 Katz NP, Sherburne S, Beach M, et al. Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. Anesth Analg 2003;97:1097–102.
44 Belgrade MJ, Ismail M, Yoon M, Panopoulos G. Non-compliant drug screens during opioid maintenance analgesia for chronic non-malignant pain. Am Pain Society Meeting, 2001. San Diego A# 787, p. 42.
45 Chapman C, Hill H. Prolonged morphine self-administration and addiction liability. Evaluation of two theories in a bone marrow transplant unit. Cancer 1989;63:1636–44.
46 Harati Y, Gooch C, Swenson M, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology 1998;50:1842–6.

47 Rangel-Guerra R. An open evaluation of oral butorphanol as long-term therapy in out-patients suffering from moderate to severe chronic pain. J Int Med Res 1981;9:120–3.
48 Manchikanti L, Vidyasagar P, Damron K, et al. Prevalence of opioid abuse in interventional pain medicine practice settings: A randomized clinical evaluation. Pain Physician 2001;4:358–65.
49 Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: A prospective cohort study. BMC Health Serv Res 2006;6:46.
50 Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain. Report of 38 cases. Pain 1986;25:171–86.
51 Dellemijn PLI, van Duijn H, Vanneste JAL. Prolonged treatment with transdermal fentanyl in neuropathic pain. J Pain Symptom Manage 1998;16:220–9.
52 Burchman SL, Pagel PS. Implementation of a formal treatment agreement for outpatient management of chronic nonmalignant pain with opioid analgesics. J Pain Symptom Manage 1995;10:556–63.
53 Arkinstall W, Sandler A, Goughnour B, et al. Efficacy of controlled-release codeine in chronic non-malignant pain: A randomized, placebo-controlled clinical trial. Pain 1995;62:169–78.
54 Broughton AN, Gordon DN, Miller AJ. Long term tolerability of cr oxycodone (OxyContin tablets) in 101 patients treated for 12 months. World Congress On Pain, 1999, 339.
55 Simpson RK Jr, Edmondson EA, Constant CF, Collier C. Transdermal fentanyl as treatment for chronic low back pain. J Pain Symptom Manage 1997;14:218–24.
56 Wan Lu C, Urban B, France RD. Long-term use of narcotic analgesics in chronic pain. Soc Sci Med 1988;19:1379–82.
57 Portenoy RK. Chronic opioid therapy for nonmalignant pain: From models to practice. APS J 1992;1:285–8.
58 Kell MJ, Musselman DL. Methadone prophylaxis of intractable headaches: Pain control and serum opioid levels. AJPM 1993;3:7–14.
59 Ytterberg SR, Mahowald ML, Woods SR. Codeine and oxycodone use in patients with chronic rheumatic disease pain. Arthritis Rheum 1998;41:1603–12.
60 Allan L, Hays H, Jensen NH, et al. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. BMJ 2001;322:1–7.
61 Cowan DT, Allan L, Griffiths P. A pilot study into the problematic use of opioid analgesics in chronic non-cancer pain patients. Int J Nurs Stud 2002; 39:59–69.
62 McIlwain H, Ahdieh H. Safety, tolerability, and effectiveness of oxymorphone extended release for moderate to severe osteoarthritis pain. A one year study. Am J Ther 2005;12:106–12.
63 Chao J. Retrospective analysis of Kadian (morphine sulfate sustained-release capsules) in patients with chronic, nonmalignant pain. Pain Med 2005;6:262–5.
64 Matsumoto A, Babul N, Ahdieh H. Oxymorphone extended-release tablets relieve moderate to severe pain and improve physical function in osteoarthritis: Results of a randomized, double-blind, placebo- and active-controlled phase III trial. Pain Med 2005;6:357–66.
65 Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: Preliminary validation of the opioid risk tool. Pain Med 2005;6:432–42.
66 Richarz A, Simpson K, Slappendel R. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naïve patients with chronic low back pain. Spine 2005;30:2484–90.
67 Watson C, Peter N, Babul N. Efficacy of oxycodone in neuropathic pain: A randomized trial in postherpetic neuralgia. Neurology 1998;50:1837–41.
68 Roth SH, Fleischman RM, Burch FX, et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain. Arch Intern Med 2000;160:853–60.
69 Markenson JA, Zhang CJ, Richards P. Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical trial. Clin J Pain 2005;21:524–35.
70 Gimbel JS, Richards P, Portenoy RK Controlled-release oxycodone for pain in diabetic neuropathy. A randomized controlled trial. Neurology 2003; 60:927–34.
71 Raja SN, Haythornthwaite JA, Pappagallo M, et al. Opioids versus antidepressants in postherpetic neuralgia. A randomized, placebo-controlled trial. Neurology 2002;59:1015–21.
72 Huse E, Larbig W, flor H, Birbaumer N. The effect of opioids on phantom limb pain and cortical reorganization. Pain 2001;90:47–55.
73 Haythornthwaite JA, Menefee LA, Quatrano-Piacentini AL, Pappagallo M. Outcome of chronic opioid therapy for non-cancer pain. J Pain Symptom Manage 1998;15:185–94.
74 Quang-Cantagrel Nathalie D, Wallace MS, Magnuson SK. Opioid substitution to improve the effectiveness of chronic noncancer pain control: A chart Review. Anesth Analg 2000;90:933–7.
75 Schofferman J. Long-term opioid analgesic therapy for severe refractory lumbar spine pain. Clin J Pain 1999;15:136–40.
76 Salzman RT, Brobyn RD. Long-term comparison of suprofen and propoxyphene in patients with osteoarthritis. Pharmacology 1983;27(suppl 1):55–64.

77 Peloso PM, Bellamy N, Bensen W, et al. Double blind randomized placebo control trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. J Rheumatol 2000;27:3.
78 Wilder-Smith CH, Hill L, Spargo K, Kalla A. Treatment of severe pain from osteoarthritis with slow-release tramadol or dihydrocodeine in combination with NSAIDs: A randomized study comparing analgesia, antinociception and gastrointestinal effects. Pain 2001;91:23–31.
79 Palangio M, Damask MJ, Morris E, et al. Combination hydrocodone and ibuprofen versus combination codeine and acetaminophen for the treatment of chronic pain. Clin Ther 2000;22:879–92.
80 Caldwell JR, Rapoport RJ, Davis JC, et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain. Results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. J Pain Symptom Manage 2002;23:278–91.
81 Mystakidou D, Parpa E, Tsilika E, et al. Long-term management of noncancer pain with transdermal therapeutic system—Fentanyl. J Pain 2003;4:298–306.
82 Watson CPN, Moulin D, Watt-Watson J, Gordon A, Eisenhoffer J. Controlled-release oxycodone relieves neuropathic pain: A randomized controlled trial in painful diabetic neuropathy. Pain 2003;105:71–8.
83 Zimmerman M, Waap I. Individual aspects of the quality of life of patients with chronic pain. Observational study of treatment with fentanyl-TTS. MMW Fortschr Med 2005;147(suppl 1):33–40.
84 Manchikanti L, Manchukonda R, Pampati V, et al. Does random urine drug testing reduce illicit drug use in chronic pain patients receiving opioids? Pain Physician 2006;9:123–9.
85 Rowbotham MC, Twilling L, Davies P, Reisner L, Taylor K, Mohr D. Oral opioid therapy for chronic peripheral and central neuropathic pain. N Engl J Med 2003;348:1223–32.
86 Parr G, Darekar B, Fletcher A, Bulpitt C. Joint pain and quality of life: Results of a randomized trial. Br J Clin Pharmacol 1989;27:235–42.
87 Rhodin A, Gronbladh L, Nilsson LH, Gordh T. Methadone treatment of chronic non-malignant pain and opioid dependence—A long-term follow-up. Eur J Pain 2006;10:271–8.
88 Adams EH, Chwiecko P, Ace-Wagoner Y, et al. A study of Avinza® (morphine sulfate extended-release capsules) for chronic moderate-to-severe noncancer pain conducted under real-world treatment conditions—The ACCPT Study. Pain Pract 2006;6:254–64.
89 Michna EJ, Ross EL, Janfaza D, et al. Urine toxicology screening among chronic pain patients on opioid therapy: Frequency and predictability of abnormal findings. Clin J Pain 2007;23:173–9.
90 Institute of Medicine Committee to advise Public Health Service on Clinical Practice. Clinical Practice Guidelines Directions for a New Program. Washington, DC: National Academy Press; 1990.
91 Hoogendoorn WE, van Poppel MN, Bongers PM et al. Systematic review of psychosocial factors at work and private life as risk factors for back pain. Spine 2000;25:2114–25.
92 De Vet H, de Bie R, vender Heijden G, et al. Systematic reviews on the basis of methodological criteria. Physiotherapy 1997;83:284–9.
93 Borghouts JA, Koes BW, Bouter LM. The clinical course and prognostic factors of non-specific neck pain: A systematic review. Pain 1998;77:1–13.
94 Kirsh K, Whitcomb L, Donaghy K, Passik S. Abuse and addiction issues in medically ill patients with pain: Attempts at clarification of terms and empirical study. Clin J Pain 2002;18:S52–60.
95 Cowan D. Problematic terminology for problematic drug use. J Opioid Manage 2006;2:23–30.
96 Fishbain DA. Chronic pain and addiction, chapter 10. In: Boswell MV, Cole BE, eds. Weiner's Pain Management, A Practical Guide for Clinicians, 7th edition. Boca Raton, FL: CRC Press; 2006:117–39.
97 Li V, Katragadda R, Mosuro Y, Friedman R. Pain and addiction: Screening patients at risk. Pain Med 2001;2:244,A216.
98 Sees K, DiMarino M, Ruediger N, Sweeney C, Shiffman S. Non-medical use of OxyContin tablets in the United States. J Pain Palliat Care Pharmacother 2005;19:13–23.
99 Smith M, Woody G. Nonmedical use and abuse of scheduled medications prescribed for pain, pain-related symptoms, and psychiatric disorders: Patterns, user characteristics, and management options. Curr Psychiatry Rep 2005;7:337–43.
100 Nurnberger J, Foroud T, Flury L, et al. Evidence for a locus on chromosome 1 that influences vulnerability to alcoholism and affective disorder. Am J Psychiatry 2001;158:718–24.
101 Passik S, Kirsh K, Whitcomb L, Dickerson P, Theobald D. Pain clinicians' rankings of aberrant drug-taking behaviors. J Pain Palliative Care 2002;16:39–49.
102 Weissman DE, Haddox JD. Opioid pseudoaddiction: An iatrogenic syndrome. Pain 1989;36:363–6.
103 Ferrari A, Cicero AF, Bertolini A, Pasciullo G, Sternieri E. Need for analgesics/drugs of abuse: A comparison between headache patients and addicts by the Leeds Dependence Questionnaire (LDQ). Cephalgia 2006;26:187–93.
104 Elander J, Lusher J, Bevan D, Telfer P, Burton B. Understanding the causes of problematic pain management in sickle cell disease: Evidence that

pseudoaddiction plays a more important role than genuine analgesic dependence. J Pain Symptom Manage 2004;27:156–69.

105 Katz N, Fanciullo GJ. Role of urine toxicology testing in the management of chronic opioid therapy. Clin J Pain 2002;18(4 suppl): S76–82.

106 Lusher J, Elander J, Bevan D, Telfer P, Burton B. Analgesic addiction and pseudoaddiction in painful chronic illness. Clin J Pain 2006;22:316–24.